Human and Ecological Risk Assessment, 21: 1644–1663, 2015
ISSN: 1080-7039 print / 1549-7860 online
DOI: 10.1080/10807039.2014.967039

The Use of Epidemiology in Risk Assessment: Challenges and Opportunities

Krista Christensen,[1] Carol H. Christensen,[2] J. Michael Wright,[3] Audrey Galizia,[1] Barbara S. Glenn,[1] Cheryl Siegel Scott,[1] Jennifer K. Mall,[1] Thomas F. Bateson,[1] Patricia A. Murphy,[4] and Glinda S. Cooper[1]

[1]National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC, USA; [2]Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, DC, USA; [3]National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Cincinnati, OH, USA; [4]National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Edison, NJ, USA

ABSTRACT

The assessment of risk from environmental and occupational exposures incorporates and synthesizes data from a variety of scientific disciplines including toxicology and epidemiology. Epidemiological data have offered valuable contributions to the identification of human health hazards, estimation of human exposures, quantification of the exposure–response relation, and characterization of risks to specific target populations including sensitive populations. As with any scientific discipline, there are some uncertainties inherent in these data; however, the best human health risk assessments utilize all available information, characterizing strengths and limitations as appropriate. Human health risk assessors evaluating environmental and occupational exposures have raised concerns about the validity of using epidemiological data for risk assessment due to actual or perceived study limitations. This article highlights three concerns commonly raised during the development of human health risk assessments of environmental and occupational exposures: (a) error in the measurement of exposure, (b) potential confounding, and (c) the interpretation of non-linear or non-monotonic exposure–response data. These issues are often the content of scientific disagreement and debate among the human health risk

This article not subject to United States copyright law.
Received 27 February 2014; revised manuscript accepted 14 September 2014.
Address correspondence to Carol H. Christensen, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, 1200 Pennsylvania Avenue NW, Mailcode 7509P, Washington, DC 20460, USA. E-mail: Christensen.Carol@epa.gov
Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/bher.

ED_002191_00025139-00001

assessment community, and we explore how these concerns may be contextualized, addressed, and often ameliorated.

Key Words: epidemiology, risk assessment, bias, measurement error, confounding, exposure–response, misclassification.

INTRODUCTION

Human health risk assessment (HHRA) is a process used to estimate the nature and probability of adverse health effects in humans who may be exposed to chemical and non-chemical stressors in environmental media (*e.g.*, air, water, soil, or food) or in the workplace (USEPA 2013). The risk assessment paradigm is comprised of four steps: hazard identification, exposure assessment, dose–response modeling, and risk characterization (NRC 1983). A risk assessment may be designed to address questions such as "What types of health problems may be caused by different environmental and occupational stressors such as chemicals, microbes, or radiation?" or "What is the probability that an adverse health effect will occur within a specific range of concentration or dose of these stressors?" The answers to these questions and others determine the scope of the human health risk assessment and influence what actions may be necessary for public health protection from environmental and occupational hazards. HHRA includes a synthesis of data from a variety of scientific disciplines including toxicology, epidemiology, industrial hygiene, and exposure science. Each of these types of scientific data has strengths as well as limitations for use in risk assessment.

Epidemiological data can provide valuable contributions to all stages of a HHRA, including hazard identification, exposure–response evaluation, and risk characterization. For several decades, different authors have extensively discussed the challenges of using epidemiological data in regulatory risk assessment—but have also emphasized the need to overcome these challenges, as human data provide unique information beyond what can be gleaned from traditional toxicology-based risk assessments (Gibb *et al.* 2002; Goldbohm *et al.* 2006; Gordis 1988; Graham *et al.* 1995; Hertz-Picciotto 1995; Johnson 2010; Lavelle *et al.* 2012; Samet *et al.* 1998; Schwartz 2002; Stayner *et al.* 2002; Whittemore 1986).

Over the past few decades, environmental epidemiology has advanced significantly, particularly with regard to exposure assessment methods, facilitating greater use of these data in risk assessment. For example, the Agricultural Health Study (AHS) developed a pesticide exposure metric for use in the prospective cohort study using data collected through self-report questionnaire (Alavanja *et al.* 1996). Exposure assessment methods developed further over the course of the follow-up of this cohort, and includes collection of additional biomonitoring data and other information to validate and improve the original algorithm (Coble et al. 2005, 2011; Thomas et al. 2010). In air pollution epidemiology, researchers and policy-makers have been working together to make best use of available time-series data to assess human health risk to particulate matter ($PM_{2.5}$) (Fann et al. 2011, 2012). In addition, researchers and policy-makers are looking beyond standard single chemical

ED_002191_00025139-00002

exposures in HHRA, and are considering the role of multiple, cumulative chemical exposures as well as non-chemical exposures such as psycho-social stressors on health (Morello-Frosch and Shenassa 2006; Sexton and Hattis 2007). Given these advancements, this is an auspicious time to re-commit to the use of epidemiology in risk assessment to improve public health. For example, human data from modern epidemiology studies can inform the identification of hazards for which an animal model does not exist. These data can also inform estimates of risk in the low range of exposure and in the species of interest, and aid in the characterization of risks in sensitive populations (Burke 1995; Hertz-Picciotto 1995; Nachman *et al.* 2011; Samet *et al.* 1998). Consequently, many federal and international agencies that perform human health risk assessment state that epidemiological data should be preferentially incorporated into risk assessments when available (USEPA 2005; IARC 2000; NRC 2009).

Despite these recommendations, epidemiological data have been used in regulatory risk assessment relatively infrequently. For example, human data have been used to support less than 10% of risk assessments in the U.S. Environmental Protection Agency's (USEPA's) Integrated Risk Information System (IRIS) program (Persad and Cooper 2008), even in instances in which human data were available and could have been used more extensively in the risk assessment (Nachman *et al.* 2011; Persad and Cooper 2008). Concerns relating to the limitations and perceived insensitivity of epidemiological methods to meet the demands of risk assessment have been raised as a rationale against greater incorporation of these data in HHRA. One major limitation of observational studies is the potential for errors in assigning exposure values to study participants, possibly leading to misclassification of exposure and biased study results. Characterization of the anticipated direction, and even the magnitude, of this potential bias may be able to address this limitation. Another challenge involves the inadequate measure or control of potentially confounding variables. We discuss how the phenomenon of (strong) confounding such that study inference is incorrect is less common than presumed in published environmental and occupational epidemiology studies, and that there are strict criteria that must be met for a variable to bias study results in this way (Blair *et al.* 2007). Lastly, another misconception is that a non-linear or non-monotonic exposure–response trend in an epidemiology study is evidence of a non-causal relationship between exposure and disease. However, research from multiple scientific disciplines has shown that many true exposure–response relations are inherently non-linear or non-monotonic in nature, the identification of which adds scientific value to the risk assessment (Conolly and Lutz 2004; Vandenberg *et al.* 2012).

Understanding and constructively addressing the challenges noted above is critical for moving the field of environmental public health forward. Observational studies of environmental and occupational exposures reflect "real world" exposure–disease associations as opposed to experimentally controlled scenarios. As such, risk assessment models will benefit from incorporating these data, when appropriate. Situations in which the epidemiological data cannot be integrated into risk models in an easy or straightforward manner will inevitably lead to informative discussion within the multi-disciplinary team. In this article, we explore how data

ED_002191_00025139-00003

from epidemiology studies can make a key contribution to understanding hazard and risk in human populations.

SPECIFIC ISSUES TO CONSIDER

Exposure Issues

Characterizing the degree to which humans come in contact with chemical, biological, radiological, or other agents in the environment or in the workplace is challenging. An accurate and precise measure of human exposure must reflect the timing, frequency, duration, and intensity of these exposures during a biologically relevant time period (*e.g.*, a lifetime cancer risk, or the period of gestational susceptibility). This may require extensive and, therefore, potentially expensive, exposure measurement efforts. The importance of these efforts is underscored by methodological research that indicates that misclassification as a result of incorrect exposure measurement likely influences bias in epidemiology studies to a far greater extent than confounding in epidemiology (Blair *et al.* 2007). The challenge of accurate and precise human exposure assessment notwithstanding, the use of human exposure information in human health risk assessment remains far superior to alternatives (*e.g.*, extrapolation from high-dose animal studies) (USEPA 2005, 2013; IARC 2000; Schwartz 2002).

Exposure assessment approaches can vary widely across occupational and environmental epidemiology studies. The type of disease or exposure under study (*e.g.*, acute or chronic), study population (occupationally or environmentally exposed), and the availability and feasibility of measurable exposure information will affect the type and quality of epidemiological exposure assessment. The extent to which epidemiology studies may contribute to a risk assessment will depend in large part on the exposure assessment. Many perceived flaws or inadequacies of epidemiology studies relate to the quality of the exposure assessment. These include the use of ecologic (group-level) versus individual-level exposure information; the grouping of exposure utilizing qualitative or semi-quantitative versus quantitative exposure categorization methods; and, the potential for error or mistakes in the measurement or classification of exposure. We posit, however, that studies using these imperfect methods may still inform risk assessment.

Assessment of Environmental and Occupational Exposures

Epidemiologists have a suite of exposure assessment approaches available to characterize human exposure to occupational and environmental agents. These include use of questionnaires; environmental or workplace measurement either alone or in combination with exposure modeling (*e.g.*, air dispersion modeling); personal or biological exposure monitoring; and use of exposure assessment tools such as job-exposure matrices. Using any of these exposure assessment methods, the actual exposure of interest (*i.e.*, the level of the agent or its active metabolite in the target tissue at the critical window of time) is rarely known with certainty, but available methods do allow the epidemiologist to rank or order participants in a study with high accuracy, thus allowing valid (unbiased) estimation of risk.

ED_002191_00025139-00004

There are a variety of ways in which exposure assessment results may be utilized to estimate risk. Qualitative exposure measures are the least information-intensive approach, followed by semi-quantitative measures; quantitative measures are generally the most information intensive. In the experience of the authors, there may be a perception that epidemiology studies utilizing qualitative or semi-quantitative methods to categorize exposure are uninformative to the risk assessment process. However, there are valid uses for these data. An example of a qualitative exposure measure would be to characterize all workers in a particular job category as exposed to a substance, and compare them to workers in a different job category, considered to be "not exposed." Often a wide variety of industrial hygiene data are used to define exposure status for specific jobs or tasks within an industry. Such exposure assignments were made by studies of exposure to perchloroethyene in the dry cleaning industry; dry cleaners were classified as exposed, and launderers were classified as unexposed (Eskenazi *et al.* 1991; Gold *et al.* 2008; Raisanen *et al.* 2001). Epidemiology studies in which exposure is based on a dichotomized categorization (*i.e.*, exposed and unexposed) can inform the potential for hazard (or harm), but cannot support evaluation of exposure–response relationships without additional sources of information. Importantly, in some instances where the database of information is limited, studies with qualitative exposure measures represent the "best available" exposure measurement approach and may provide the only human data on an important public health issue.

Semi-quantitative exposure measures may also be used in epidemiology studies. These measures reflect more detailed information on each subject's individual exposure than qualitative methods and allow for an ordinal categorization (*e.g.*, low, medium, high) based on knowledge of a variety of factors including duration, frequency, and intensity of exposure, or based on knowledge of relative exposures in different types of jobs. The use of semi-quantitative exposure categories of increasing magnitude provides stronger evidence of a human health hazard than strictly qualitative (*e.g.*, none, low, or high) approaches and in some cases would allow evaluation of the relative exposure–response relationship.

Quantitative exposure classification can increase the accuracy of exposure estimates and should most closely represent the "true" (human) exposure experience. However, it should be emphasized that quantitative estimates (*e.g.*, individual air concentrations of a chemical during an 8-hour work shift, or individual biomarkers of a chemical) are not necessarily the "true" exposure of interest, but still a surrogate for this generally unknowable value. With that said, in addition to adding to the body of evidence in a hazard identification evaluation, studies with quantitative exposure data may inform the exposure-assessment phase of a risk assessment for a specific target population and may be used to estimate exposure–response relationships in greater detail for an exposed population.

A common misperception of environmental epidemiology studies is that they must include individual-level, quantitative exposure information in order to accurately characterize exposure for use in risk assessment. However, even with a complete lack of individual-level quantitative exposure measurements (*i.e.*, only group-level data are available), it may still be possible to apply externally derived exposure data for the characterization of risk. For example, external information

ED_002191_00025139-00005

sources such as predictive models of exposure, literature-based exposure databases, or geographical information systems may be used to verify exposure trends observed on the group level, and even to develop individual-level exposure estimates in qualitative or semiquantitative categories (Henn *et al.* 2010; Ritz and Costello 2006; Teschke *et al.* 2002).

In summary, there are many ways to assess environmental exposures in epidemiology studies, each with inherent strengths and weaknesses. Even relatively crude qualitative measures of exposure such as "ever" or "never" exposed can be useful in identifying hazards associated with an exposure, and semi-quantitative and quantitative measures can further be used to support exposure–response analyses. In the next section, we discuss the implications of errors in the measurement of exposure, and the ability to correctly discern the magnitude and direction of the risk estimate despite these potential errors.

Exposure Measurement Error and Effect on Exposure–Outcome Associations

As described above, epidemiologists aspire to have exact dose or quantitative exposure information on each individual in the study population, but often this information is not feasible to obtain. Thus, nearly all exposure estimates are approximations or surrogates of delivered dose and are assumed to reflect some degree of error and misclassification (Smith 2002). Conceptually, it is useful to consider exposure measurement error in epidemiology studies as the difference between the "ideal" and the "actual" exposure estimate. The "error" is the difference between what epidemiologists would like to ideally measure and what is practically feasible to measure (Savitz 2003). Different types of measurement error can arise from a variety of sources. Some of these sources include analytical limitations (such as limited sensitivity of exposure measurement instruments resulting in more uncertainty in concentration measurements), sampling from a non-representative time period, and missing data. Appreciation of the different types of measurement error, and their effects on epidemiological measures of association, is critical in judging the influence of measurement error on the validity of the study as well as upon the utility of a study to assess the relationship between exposure and health outcomes. In the authors' experience, many perceive that an error in measurement renders the results of an epidemiology study unusable or unreliable. While that may be true in some instances, much of the time the magnitude and direction of the error can be predicted or characterized to allow accurate epidemiological inference (Smith 1988).

Measurement error is classified as either differential or non-differential with reference to the other comparison group. Non-differential error refers to an exposure assessment error that is independent of the health outcome status of the participants. Differential error occurs when the error is dependent on a person's outcome status. Recall bias is an example of this, where individuals with disease may remember more details about previous exposures than healthy individuals in a case-control study, or conversely the illness being examined may interfere with the ability of an individual to recall and report information on past exposures. The manner in which the misclassification is related to the disease outcome of interest influences the confidence in the resulting effect estimate.

ED_002191_00025139-00006

Exposure misclassification bias can influence risk estimates derived from epidemiology studies, but the potential for error of this nature does not preclude the use of an epidemiology study for human health risk assessment. It is generally understood that in most instances, although there are some exceptions, non-differential error in exposure measurements (where the exposure error is independent of the health outcome status) for a dichotomized exposure results in an attenuation of the observed effect (*i.e.*, bias toward the null value of the measure of association) as well as inaccurate estimates of the precision of epidemiological effect estimates (*i.e.*, the standard error estimates are artificially small) (Blair *et al.* 2007; Deddens and Hornung 1994; Deklerk *et al.* 1989). However, this is not always true for continuous exposure measures, depending on the nature of the measurement error (*e.g.*, Berksonian bias; Armstrong 1990). Non-differential exposure measurement error in otherwise well-conducted epidemiology studies, while undesirable, would generally not be expected to create a false positive association (Correa-Villasenor *et al.* 1995; Jurek *et al.* 2008). That is, if the true odds ratio was actually 1.0 (no association between exposure and outcome), non-differential exposure measurement error is an unlikely explanation of a higher observed odds ratio such as 2.0. Sensitivity analyses such as assessing the effect estimates in relation to varying proportions of study participants presumed to be misclassified would aid characterization of this uncertainty in risk assessment. If the investigator has some knowledge about the exposure measurement error, statistical inferences may also be directly adjusted to account for this error (Stayner *et al.* 2007).

Exposure estimates may also be evaluated as quantitative measure (continuous data) or semi-quantitative (use of categorical variables). Classification of exposure using an ordinal scale (such as 1, 2, and 3 for low, medium, and high exposure) can be particularly useful for hazard identification or assessing relative trends but may be of limited use for quantifying exposure–response relationships, particularly if assumptions regarding homogeneous exposure and risk within these categories are not met. Misclassification bias is a particular concern when continuous exposure data are split into categories. For example, an unexposed participant may be mistakenly classified as exposed based on an arbitrary dichotomous exposure cut-point. Errors in exposure categorization can occur as a result of errors in data collection or data entry, failure to recall an exposure in a self-reported exposure questionnaire, or reliance on current exposure information as a proxy for exposures in the past, among others factors. Misclassification into adjacent categories is more likely than across several levels (*i.e.*, between medium and high exposure versus low and high exposure), and this misclassification can result in biased and imprecise study results.

In summary, while errors in classifying exposures of individual study participants occurs, methodological research into the effects of different types of classification errors allows informed epidemiological (causal) inference. Therefore, even when exposure measurement error is present, epidemiological data can still provide valuable information for risk assessment. Information is often available in epidemiology studies that can help characterize the direction or magnitude of errors to estimate their impact on the association between exposure and health outcome. Such information may come from the broader literature on exposure assessment, from methods papers on the study in question, or from supplemental information from the researchers (such as that found in appendices or online supplements). These

ED_002191_00025139-00007

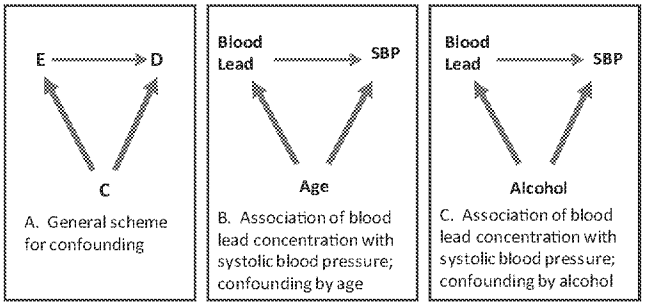

Figure 1. Panel A: Graphical depiction of general scheme for required relationships between exposure (E), disease (D), and potential confounder (C). Panels B and C depict the association of blood lead concentration with systolic blood pressure and potential relationships with age and alcohol consumption. Age and alcohol consumption both are associated with increases in blood lead concentration (Falq *et al.* 2011; Hense *et al.* 1992; Lee *et al.* 2005) and with systolic blood pressure (Marchi *et al.* 2014; Scinicariello *et al.* 2011). However, alcohol, primarily wine, contains lead (Ajtony *et al.* 2008), and adjustment for this source of lead exposure may remove its contribution to the variation in blood lead concentration. Thus, decisions regarding what confounders to adjust for can be complicated.

other sources of information may help clarify exposure-related issues, and thereby aid in the use of these studies for risk assessment (Fann *et al.* 2011). Although limitations in exposure assessment remains a challenge (Bailer 1999; Gordis 1988; Graham *et al.* 1995), the uncertainty in exposure measurement in epidemiology studies is likely to be small in comparison to the uncertainty in extrapolating from high doses in experimental animals to the complex human experience (Hertz-Picciotto 1995; Schwartz 2002; Smith 1988).

CONFOUNDING

Valid epidemiology studies must ensure that risk estimates from the factors (exposures) of primary interest are not unduly influenced by the presence of other risk factors, also known as confounders. Most of the major health outcomes influenced by exposure to environmental chemicals have several contributing causes (*i.e.*, multifactorial etiology) and may cluster within specific groups defined by common characteristics such as age, sex, race, socioeconomic status, or lifestyle. It is, therefore, important to account for potential differences in these factors between groups being compared (e.g., cases and controls, exposed and unexposed).

As illustrated in Figure 1, Panel A, confounders are factors that are: (1) associated *both* with the outcome, (2) *and also* with the exposure, (3) *but* do not mediate the effect of the exposure on the disease process (*i.e.*, be an intermediary factor in the causal pathway) (Szklo and Nieto 2004). All three criteria must be met for a variable to potentially confound the exposure–outcome association. For example, previous

ED_002191_00025139-00008

studies indicate that age and alcohol consumption are potential confounders of the association between blood lead concentration and systolic blood pressure because both factors are associated with exposure and outcome (Falq *et al.* 2011; Hense *et al.* 1992; Lee *et al.* 2005; Marchi *et al.* 2014; Scinicariello *et al.* 2011). Decisions about confounding can be complicated, however; in this example, alcohol consumption can be a source of lead exposure (Ajtony *et al.* 2008). Therefore, adjustment for alcohol consumption could remove some of the contribution to the increased risk of high blood pressure due to blood lead concentration.

The potential for confounding including the inadequate control of confounding (known as residual confounding) is often noted as an impediment to the use of epidemiology studies in the evaluation of hazard and risk of an environmental agent (Hertz-Picciotto 1995). Studies will often not evaluate confounding by every possible known or hypothesized risk factor, in some cases simply because new or newly suspected risk factors may be identified after a study was completed. Although many factors may be suspected confounders, it is important to examine the available data (including previous studies on the same exposure and/or outcome) to determine if confounding is truly a concern. In many instances, suspected confounding variables are not truly confounding the exposure–disease relation under study because they do not meet the aforementioned requisite three criteria for confounding.

The Evaluation of Confounding

To address potential confounding in epidemiology studies, efforts are needed to ensure that comparison groups (*e.g.*, exposed and unexposed, cases and controls) are as similar as possible with the exception of the factor being evaluated (Savitz 2003). Some epidemiology and toxicology studies attempt to control for potential confounders through the randomization step of the experimental design (*i.e.*, similar distribution of potential confounders across animal exposure groups) (Festing and Altman 2002). Since randomization is not generally feasible in occupational or environmental epidemiology studies, potential confounding can be addressed through study design and statistical analysis. Potential confounders, such as age, sex, and race, are often controlled by techniques such as defining exclusion/inclusion criteria for subject recruitment, matching during study design and recruitment, or restriction in the data collection or analysis phases. For example, if age is suspected to be a confounder of a chemical being studied, a study might include only those in a certain age range, or exposed and unexposed participants might be matched by age or age group (Aschengrau and Seage 2003; Last 2001). These design features allow investigators to select study subjects so that potential confounders are distributed more equally among exposed and unexposed groups.

When appropriate data have been collected, potential confounders also can be controlled for during the data analysis phase by such methods as standardization, stratification, or statistical modeling. Standardization and stratification are two methods that can be used to develop a summary risk estimate while accounting for differences between comparison groups with respect to potential confounding characteristics (Aschengrau and Seage 2003; Rothman *et al.* 2008). The particular method

ED_002191_00025139-00009

or methods selected to control for confounding are determined by the type of data available. For example, if vital statistics data (such as national or state mortality rates) are examined, then standardization can be used to control for confounding by comparing rates in the population under study with the rates in the general population using the same distributions for age, sex, and race. Controlling for confounding also can be achieved through statistical adjustment in multivariate models, a technique that easily allows simultaneous adjustment or stratification for several variables (Aschengrau and Seage 2003). In effect, statistical adjustment for confounding creates strata of individuals with similar values of the confounder for analysis. If the effect estimates are meaningfully different when potential confounders are included or not included in the model, then confounding may be present (often a difference of roughly +/– 10% in the effect estimate is considered evidence of confounding). The ability to meaningfully adjust for confounders in an analysis is dependent on the quality of the data, including the amount and type of measurement error in the confounding variables that are being examined.

Although statistical modeling is a powerful tool for addressing potential confounding, it is necessary to carefully select the factors to include in the exposure–response models, rather than including every possible variable or to rely solely on statistical criteria to determine which variables may be potential confounders. This is important because including extraneous risk factors in a regression can reduce precision and even produce unintended confounding due to the interrelationship of the included covariates, resulting in a biased effect estimate. Causal diagrams may be useful in judging whether including certain potential confounders in the model is necessary (Greenland *et al.* 1999; Hernandez-Diaz *et al.* 2008). For a more complete explanation of the use of causal diagrams in modeling decisions, see these citations: Howards *et al.* (2012), Schisterman *et al.* (2009), and VanderWeele (2009).

Influence of Confounding on Effect Estimates

If a confounder is identified as a concern during the planning of a study, the control of potential confounding may be relatively straightforward through aspects of the design and analysis described above. Evaluating the role of confounding for factors not considered in the design is more difficult, but still possible. The first consideration is whether there is any evidence to suggest potential confounding and, if so, its influence (direction and magnitude) on the risk estimate. Recall that all three criteria must be met (confounder must be associated with both the outcome of interest and with the exposure, but the confounder must not mediate the effect of the exposure on the disease process) in order for a variable to have a potential confounding effect on the exposure–outcome relation of interest (Szklo and Nieto 2004). When all of the aforementioned three conditions for confounding are met, the magnitude and direction of the bias depends on the strength and direction of the associations between the confounder and both the exposure and also the outcome of interest in a particular study, as well as the prevalence of the confounder in the population of interest.

For a confounder to fully explain the association between exposure and outcome, the confounder must have as great an influence on the relative risk of the

ED_002191_00025139-00010

outcome as the exposure of interest. For example, analyses of confounding in occupational studies have found that the associations of smoking with both exposure and outcome must be moderately to strongly correlated before there is a change in the estimated risk for the outcome (Blair *et al.* 2007; Kriebel *et al.* 2004). Even for studies of occupational exposures and lung cancer risks, analyses that adjusted for smoking rarely found that the adjusted relative risk was substantially different from the unadjusted relative risk (*i.e.*, odds ratios differed by no more than 0.3 in the studies evaluated; Blair et al. 2007). Researchers concluded that in the occupational studies they evaluated, relative risks for lung cancer of 1.5 or higher are unlikely to be entirely explained by uncontrolled confounding by smoking behavior (Axelson and Steenland 1988). This is because the distribution of nonsmokers, moderate and heavy smokers must be very different between the exposed group and comparison population for smoking to substantially change the effect estimate.

Concerns about the influence of confounding on observed effect estimates may arise for studies involving populations exposed to more than one chemical or pollutant at a time. Co-exposures with moderate correlation should be considered as potential confounders in statistical models, if they also are risk factors for the health outcome under study and are not part of the exposure-to-response trajectory (*i.e.*, mediators in the causal pathway). Use of multi-variable regression techniques or other statistical tools such as factor analysis can isolate the exposure–disease association of interest, while controlling for the effect of co-exposures. In addition, if more than one study is available to evaluate the exposure–response relationship, then consistency in the collection of studies, including those that did or did not adjust for a particular co-exposure, can help determine if confounding by a specific co-exposure is likely. Although every individual is exposed to many agents, both chemical and non-chemical stressors, via various routes (oral, inhalation, dermal), it is likely that only a small subset of possible exposures would both be correlated with the exposure of interest, and also be risk factors for the health outcome of interest. Recall that both associations must be present at moderately strong correlations for confounding to occur. For example, Patel *et al.* (2012) found that in the National Health and Nutrition Examination Survey, biomarkers of exposure were generally not strongly correlated with each other; exceptions included compounds in the same chemical family (*e.g.*, polychlorinated biphenyls) that generally occur as mixtures in environmental media (Patel *et al.* 2012).

When a study population is exposed to multiple agents, and these exposures are highly correlated (*e.g.*, $\rho > .80$), it may be difficult to analytically disentangle individual exposure effects. This issue has been encountered in studies of many environmental contaminants, including air pollutants (Bell *et al.* 2007, 2009), drinking water contaminants (Rivera-Núñez and Wright 2013), and certain pesticides (Alavanja *et al.* 2003; Bell *et al.* 2007, 2009). In this situation, confounding may be difficult to address with statistical analysis. However, one may be able to draw insights from studies in other locations or exposure scenarios where the correlation between the same or similar agents is lower (Bell *et al.* 2011). When two or more agents are always encountered together, evaluating the risk of the combined exposure is a relevant consideration for public health since they better reflect real-world exposure

ED_002191_00025139-00011

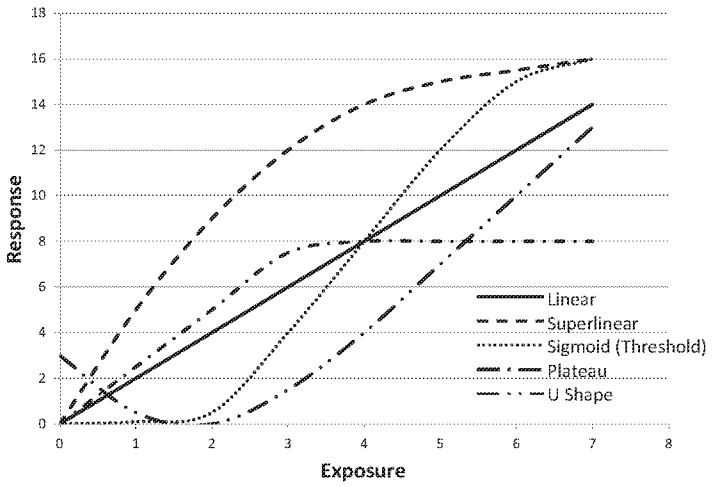

Figure 2. Examples of different exposure–response curves.

mixture scenarios and can offer some insight into potential combined effect of multiple exposures on human health.

THE EXPOSURE–RESPONSE RELATIONSHIP

The relation between environmental or occupational exposures and human diseases may take many different forms (linear or non-linear) (Figure 2). Critics may question the internal validity of an epidemiology study and its utility for quantitative risk assessment when the observed exposure–response relationship is not linear, or even non-monotonic. However, the observation of a non-monotonic curve in an individual study may be biologically plausible and can be used to inform a risk assessment (Wigle and Lanphear 2005). Further, the shape of the exposure–response relationship observed in a given study may depend on numerous factors including: population characteristics, the statistical model used, range of exposure, statistical power, and, as discussed previously, other factors including exposure measurement error (Brauer *et al.* 2002; Park and Stayner 2006). Consideration as to whether an observed exposure–response curve is a true representation of the underlying relation or an artifact of study design or conduct (*e.g.*, unbalanced observations per exposure category) requires expert consideration of many different factors.

The simplest exposure–response curve shape is linear, in which level of exposure is directly proportional to level of response. This type of relationship has been seen, for example, in epidemiology studies of methylmercury exposure and effects on neurodevelopment (NRC 2000). However, non-linear exposure–response curves are often observed in environmental and occupational epidemiology studies. A supra-linear relation in which exposure–response is linear at lower doses but attenuated at high doses, leading to an observed response plateau, is a frequently observed phenomenon in epidemiology (Blair *et al.* 1998; Cocco *et al.* 2001; Gibb *et al.* 2000; Hayes *et al.* 1996; Hertz-Picciotto and Smith 1993; Hornung and Meinhardt 1987;

ED_002191_00025139-00012

Schubauer-Berigan *et al.* 2011; Stayner *et al.* 1993; Steenland *et al.* 1998, 1999, 2001). For example, birth weight and neurodevelopmental measures both have been observed to have a supralinear relationship with maternal and children's blood lead levels less than 10 μg/ml, respectively (Tellez-Rojo *et al.* 2006; Zhu *et al.* 2010). This plateau in the response curve may be due to factors such as exposure misclassification or a depletion of susceptible individuals in the population, or may represent a true biological phenomenon, such as receptor saturation or enzyme depletion (Stayner *et al.* 2003). Non-linearity may also arise in groups due to different exposure profiles, such as higher intensity and shorter duration of exposure, compared with lower intensity and longer duration (Lubin *et al.* 2008).

Another type of exposure–response relationship is a "U-shaped" curve in which the exposure–response association is lower in the mid-exposure range than at either the low or high ends of the exposure range. For example, both low and high levels of exposure to manganese in early life is related to risk of adverse neurodevelopmental effects, while exposures in the mid-range are not associated with these effects (Henn *et al.* 2010). Similarly, a U-shaped association between cadmium exposure and peripheral artery disease has been shown among non-smoking women (Tellez-Plaza *et al.* 2010).

Exposure–response relations may also exhibit an apparent threshold effect. This has been observed in the relation between PCBs exposure and neuropsychological function (Haase *et al.* 2009), where no response is observed below a certain dose (possibly due to compensatory mechanisms or lack of statistical power), but the exposure–response association is significant above a certain level of exposure. In epidemiology, as in experimental toxicology studies, however, it is difficult to detect effects at low exposures, and thus it is often difficult to establish the presence or absence of thresholds.

A statistical trend test is often used to examine the change in response over an entire range of exposures. For categorical analyses, differences in effect levels are compared between exposure groups. Statistically significant effect estimates may be observed in the highest exposure categories, with smaller and non-statistically significant effect estimates observed in the intermediate and/or lower exposure categories. This may be incorrectly interpreted to mean that the "trend" only starts at the point that statistical significance is reached, or, if statistical significance is not achieved for any exposure category, that there is an absence of an association between exposure and outcome. It may be the case that a monotonic trend is present, but statistical testing of individual grouped categories does not have sufficient power to demonstrate statistical significance compared to the more powerful trend test. As noted previously, misclassification of exposure and confounding variables may also result in bias, the result of which may be an inability to detect a true exposure–response relationship.

As noted above, several factors related to exposure and response can influence the observed relationship between the two factors. First, the range of exposures evaluated affects the shape of the curve. For example, no association may be observed if exposures in the study population were very low or were very similar among all study participants; however, an increasing trend in risk may exist over a wider exposure range. For categorical exposure comparisons, the choice of the

ED_002191_00025139-00013

referent group (*i.e.*, the unexposed or a combination of those with no and low exposure) also affects comparisons made with higher exposure levels and can alter the exposure–response relationships (Stewart and Correa-Villasenor 1991). If there are positive associations at low exposure levels, inclusion of individuals with low to moderate exposure in the referent group (either by study design or due to exposure misclassification) can greatly influence effect estimates for the upper exposure categories, and decrease the slope of the observed exposure–response curve. Similarly, decisions as to how to categorize the exposure groups (*e.g.*, quartiles, or any exposure versus none) may affect the observed exposure–response relationship (Greenland 1995; Schulz *et al.* 2001; Van Wijngaarden 2005). For example, if the range within each exposure category is too broad the overall relationship may be obscured.

Exposure measurement error introduces variation and can lead to bias in the observed exposure–response relationship. For example, when exposure is classified into more than two categories, non-differential misclassification of those with the highest exposure into the lowest exposure group and vice versa, could result in a systematic bias in the observed risk estimates, and incorrectly influence the direction of a trend across exposure categories (Dosemeci *et al.* 1990). In addition, the response may also vary depending on such factors as the timing and dose of exposure, genetic susceptibility, and other factors that can influence absorption, metabolism and excretion rates across individuals; such variation will affect the shape of the exposure–response curve in a given population (Rothman 1976).

In summary, certain environmental and occupational exposure–response trends may truly be non-linear or non-monotonic in nature. Therefore, the observation of a non-linear exposure–response relationship is not necessarily an indicator of a flaw in the study. Studies that report such non-linear curves can be informative and should not be dismissed; they may provide information on both hazard identification and exposure–response. Users of such epidemiological data can gain further insight into the reported relationships by graphing or plotting the curve when such data are available to do so. Such visual representation yields information on the range of the data overall and within each group, as well as the magnitude of differences between the groups. Additionally, interpretation of other evidence including mechanistic understanding of the key biological events can provide further insight on the shape of exposure–response curves and inform causal inference.

CONCLUSION

Epidemiological data provide valuable contributions to all stages of health risk assessment, and should be used whenever possible to help reduce uncertainty in risk estimates. This article outlined some considerations when using epidemiological data for risk assessment, relating to exposure measurements, confounding, and the shape of the observed exposure–response relationship. The improvements in epidemiological methods seen in studies published in recent years make this an auspicious time to re-commit to the use of epidemiology in risk assessment to improve public health.

ED_002191_00025139-00014

DISCLAIMER

The views expressed in this article are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency or the Federal government.

ACKNOWLEDGMENT

The authors thank Dr. Aaron Blair, National Cancer Institute and Dr. Thomas Luben, U.S. Environmental Protection Agency, for their helpful review of this article.

REFERENCES

Ajtony Z, Szoboszlai N, Susko EK, *et al.* 2008. Direct sample introduction of wines in graphite furnace atomic absorption spectrometry for the simultaneous determination of arsenic, cadmium, copper and lead content. Talanta 76(3):627–34

Alavanja MC, Sandler DP, McMaster SB, *et al.* 1996. The agricultural health study. Environ Health Perspect 104(4):362–9

Alavanja MCR, Samanic C, Dosemeci M, *et al.* 2003. Use of agricultural pesticides and prostate cancer risk in the agricultural health study cohort. Am J Epidemiol 157(9):800–14

Armstrong BG. 1990. The effects of measurement errors on relative risk regressions. Am J Epidemiol 132(6):1176–84

Aschengrau A and Seage GR. 2003. Essentials of Epidemiology in Public Health. Jones & Bartlett Publishers Sudbury, MA, USA

Axelson O and Steenland K. 1988. Indirect methods of assessing the effects of tobacco use in occupational studies. Am J Indust Med 13(1):105–18

Bailer AJ. 1999. Uncertainty in risk assessment. Current efforts and future hopes. Ann NY Acad Sci 895:367–72

Bell ML, Kim JY, and Dominici F. 2007. Potential confounding of particulate matter on the short-term association between ozone and mortality in multisite time-series studies. Environ Health Persp 115(11):1591–5

Bell ML, Ebisu K, Peng RD, *et al.* 2009. Hospital admissions and chemical composition of fine particle air pollution. Am J Resp Crit Care 179(12):1115–20

Bell ML, Ebisu K, and Peng RD. 2011. Community-level spatial heterogeneity of chemical constituent levels of fine particulates and implications for epidemiological research. J Expo Sci Env Epid 21(4):372–84

Blair A, Stewart PA, Zaebst DD, *et al.* 1998. Mortality of industrial workers exposed to acrylonitrile. Scand J Work Env Hea 24:25–41

Blair A, Stewart P, Lubin JH, *et al.* 2007. Methodological issues regarding confounding and exposure misclassification in epidemiological studies of occupational exposures. Am J Indust Med 50(3):199–207

Brauer M, Brumm J, Vedal S, *et al.* 2002. Exposure misclassification and threshold concentrations in time series analyses of air pollution health effects. Risk Anal 22(6):1183–93

Burke TA. 1995. The proper role of epidemiology in regulatory risk assessment: A regulators perspective. In: Graham JD (ed), The Role of Epidemiology in Regulatory Risk Assessment., Elsevier Publishers Inc., New York, NY, USA

Coble J, Arbuckle T, Lee W, *et al.* 2005. The validation of a pesticide exposure algorithm using biological monitoring results. J Occupat Environ Hyg 2(3):194–201

ED_002191_00025139-00015

Coble J, Thomas KW, Hines CJ, *et al.* 2011. An updated algorithm for estimation of pesticide exposure intensity in the agricultural health study. International J Environ Res Public Hlth 8(12):4608–22

Cocco P, Rice CH, Chen JQ, *et al.* 2001. Lung cancer risk, silica exposure, and silicosis in Chinese mines and pottery factories: The modifying role of other workplace lung carcinogens. Am J Indust Med 40(6):674–82

Conolly RB and Lutz WK. 2004. Nonmonotonic dose-response relationships: Mechanistic basis, kinetic modeling, and implications for risk assessment. Toxicol Sci 77(1): 151–7

Correa-Villasenor A, Stewart WF, Franco-Marina F, *et al.* 1995. Bias from nondifferential misclassification in case-control studies with three exposure levels. Epidemiology 6(3):276–81

Deddens JA and Hornung R. 1994. Quantitative examples of continuous exposure measurement errors that bias risk estimates away from the null. In: Smith CM, Christiani DC, and Kelsey KT (eds), Chemical Risk Assessment of Occupational Health: Current Applications, Limitations, and Future Prospects, pp 77–85. Auburn House, Westport, CT, USA

Deklerk NH, English DR, and Armstrong BK. 1989. A review of the effects of random measurement error on relative risk estimates in epidemiological-studies. Internat J Epidemio 18(3):705–12

Dosemeci M, Wacholder S, and Lubin JH. 1990. Does nondifferential misclassification of exposure always bias a true effect toward the null value? Am J Epidemiol 132(4): 746–8

Eskenazi B, Wyrobek AJ, Fenster L, *et al.* 1991. A study of the effect of perchloroethylene exposure on semen quality in dry cleaning workers. Am J Indust Med 20(5): 575–91

Falq G, Zeghnoun A, Pascal M, *et al.* 2011. Blood lead levels in the adult population living in France the French Nutrition and Health Survey (ENNS 2006-2007). Environ Internat 37(3):565–71

Fann N, Bell ML, Walker K, *et al.* 2011. Improving the linkages between air pollution epidemiology and quantitative risk assessment. Environ Health Perspect 119(12):1671–5

Fann N, Baker KR, and Fulcher CM. 2012. Characterizing the PM(2).(5)-related health benefits of emission reductions for 17 industrial, area and mobile emission sectors across the U.S. Environ Internat 49:141–51

Festing MF and Altman DG. 2002. Guidelines for the design and statistical analysis of experiments using laboratory animals. ILAR Journal/National Research Council, Institute of Laboratory Animal Resources 43(4):244–58

Gibb HJ, Lees PSJ, Pinsky PF, *et al.* 2000. Lung cancer among workers in chromium chemical production. Am J Indust Med 38(2):115–26

Gibb HJ, Checkoway H, and Stayner L. 2002. Improving risk assessment: Priorities for epidemiologic research. Hum Ecol Risk Assess 8(6):1397–404

Gold LS, De Roos AJ, Waters M, *et al.* 2008. Systematic literature review of uses and levels of occupational exposure to tetrachloroethylene. J Occupat Environ Hyg 5(12): 807–39

Goldbohm RA, Tielemans ELJP, Heederik D, *et al.* 2006. Risk estimation for carcinogens based on epidemiological data: A structured approach, illustrated by an example on chromium. Regul Toxicol Pharm 44(3):294–310

Gordis L (ed). 1988. Epidemiology and Health Risk Assessment, Oxford University Press, New York, NY, USA

Graham J, Paustenbach D, and Butler W. 1995. Epidemiology and risk assessment: Divorce or marriage? In: Graham JD (ed), The Role of Epidemiology in Regulatory Risk Assessment, pp. 1–14. Elsevier Publishers Inc., New York, NY, USA

ED_002191_00025139-00016

Greenland S. 1995. Dose-response and trend analysis in epidemiology—Alternatives to categorical analysis. Epidemiology 6(4):356–65

Greenland S, Pearl J, and Robins JM. 1999. Causal diagrams for epidemiologic research. Epidemiology 10(1):37–48

Haase RF, McCaffrey RJ, Santiago-Rivera AL, *et al.* 2009. Evidence of an age-related threshold effect of polychlorinated biphenyls (PCBs) on neuropsychological functioning in a Native American population. Environ Res 109(1):73–85

Hayes RB, Yin SN, Dosemeci M, *et al.* 1996. Mortality among benzene-exposed workers in China. Environ Health Persp 104:1349–52

Henn BC, Ettinger AS, Schwartz J, *et al.* 2010. Early postnatal blood manganese levels and children's neurodevelopment. Epidemiology 21(4):433–9

Hense HW, Filipiak B, Novak L, *et al.* 1992. Nonoccupational determinants of blood lead concentrations in a general population. Internat J Epidemiol 21(4): 753–62

Hernandez-Diaz S, Wilcox AJ, Schisterman EF, *et al.* 2008. From causal diagrams to birth weight-specific curves of infant mortality. Eur J Epidemiol 23(3):163–6

Hertz-Picciotto I. 1995. Epidemiology and quantitative risk assessment: A bridge from science to policy. Am J Public Health 85(4):484–91

Hertz-Picciotto I and Smith AH. 1993. Observations on the dose-response curve for arsenic exposure and lung-cancer. Scand J Work Env Hea 19(4):217–26

Hornung RW and Meinhardt TJ. 1987. Quantitative risk assessment of lung-cancer in United-States uranium miners. Hlth Physics 52(4):417–30

Howards PP, Schisterman EF, Poole C, *et al.* 2012. "Toward a clearer definition of confounding" revisited with directed acyclic graphs. Am J Epidemiol 176(6):506–11

IARC (International Agency for Research on Cancer). 2000. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Ionizing Radiation, Part 1: X- and Gamma (g)-Radiation, and Neutrons. Lyon, France. Available at http://monographs.iarc.fr/ENG/Monographs/vol75/mono75.pdf (accessed July 15, 2013)

Johnson BL. 2010. The vital importance of epidemiology in risk assessment. Hum Ecol Risk Assess 16(4):669–72

Jurek AM, Greenland S, and Maldonado G. 2008. How far from non-differential does exposure or disease misclassification have to be to bias measures of association away from the null? Internat J Epidemiol 37(2):382–5

Kriebel D, Zeka A, Eisen EA, *et al.* 2004. Quantitative evaluation of the effects of uncontrolled confounding by alcohol and tobacco in occupational cancer studies. Internat J Epidemio 33(5):1040–5

Last JM. 2001. A Dictionary of Epidemiology, 4th edit. Oxford University Press, New York, NY, USA

Lavelle KS, Robert Schnatter A, Travis KZ, *et al.* 2012. Framework for integrating human and animal data in chemical risk assessment. Regul Toxicol Pharm 62(2):302–12

Lee MG, Chun OK, and Song WO. 2005. Determinants of the blood lead level of US women of reproductive age. J Am Coll Nutrit 24(1):1–9

Lubin JH, Moore LE, Fraumeni JF, Jr., et al. 2008. Respiratory cancer and inhaled inorganic arsenic in copper smelters workers: A linear relationship with cumulative exposure that increases with concentration. Environ Health Perspect 116(12):1661–5

Marchi KC, Muniz JJ, and Tirapelli CR. 2014. Hypertension and chronic ethanol consumption: What do we know after a century of study? World J Cardiol 6(5):283–94

Morello-Frosch R and Shenassa ED. 2006. The environmental "Riskscape" and social inequality: Implications for explaining maternal and child health disparities. Environ Health Persp 114(8):1150–3

ED_002191_00025139-00017

Nachman KE, Fox MA, Sheehan MC, *et al.* 2011. Leveraging epidemiology to improve risk assessment. The Open Epidemio J 4:3–29

NRC (National Research Council). 1983. Risk Assessment in the Federal Government: Managing the Process. The National Academies Press, Washington, DC, USA

NRC. 2000. Toxicological Effects of Methylmercury. Washington, DC, USA. Available at http://www.nap.edu/openbook.php?isbn=0309071402 (accessed July 15, 2013)

NRC. 2009. Science and Decisions: Advancing Risk Assessment. National Research Council (U.S.). Committee on Improving Risk Analysis Approaches Used by the U.S. EPA, Washington, DC, USA. Available at http://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment (accessed July 15, 2013)

Park RM and Stayner LT. 2006. A search for thresholds and other nonlinearities in the relationship between hexavalent chromium and lung cancer. Risk Anal 26(1): 79–88

Patel CJ, Cullen MR, Ioannidis JP, *et al.* 2012. Systematic evaluation of environmental factors: Persistent pollutants and nutrients correlated with serum lipid levels. Internat J Epidemiol 41(3):828–43

Persad AS and Cooper GS. 2008. Use of epidemiologic data in Integrated Risk Information System (IRIS) assessments. Toxicol Appl Pharmacol 233(1):137–45

Raisanen J, Niemela R, and Rosenberg C. 2001. Tetrachloroethylene emissions and exposure in dry cleaning. J Air Waste Manage Assoc 51(12):1671–5

Ritz B and Costello S. 2006. Geographic model and biomarker-derived measures of pesticide exposure and Parkinson's disease. Living in a Chemical World: Framing the Future in Light of the Past 1076:378–87

Rivera-Núñez Z and Wright JM. 2013. Associations between trihalomethane and haloacetic acid exposure and fetal growth and preterm delivery. J Occupat Environ Med 55(10):1125–34

Rothman KJ. 1976. Causes. Am J Epidemiol 104(6):587–92

Rothman KJ, Greenland S, and Lash TL. 2008. Modern Epidemiology, 3rd edit. Lipincott Williams and Wilkins, Philadelphia, PA, USA

Samet JM, Schnatter R, and Gibb H. 1998. Epidemiology and risk assessment. Am J Epidemiol 148(10):929–36

Savitz DA. 2003. Interpreting Epidemiologic Evidence: Strategies for Study Design and Analysis. Oxford University Press, Oxford, UK

Schisterman EF, Cole SR, Platt RW. 2009. Overadjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiology 20(4):488–95

Schubauer-Berigan MK, Deddens JA, Couch JR, *et al.* 2011. Risk of lung cancer associated with quantitative beryllium exposure metrics within an occupational cohort. Occupat Environ Med 68(5):354–60

Schulz MR, Hertz-Picciotto I, Van Wijngaarden E, *et al.* 2001. Dose-response relation between acrylamide and pancreatic cancer. Occupat Environ Med 58(9):609

Schwartz J. 2002. The use of epidemiology in environmental risk assessment. Hum Ecol Risk Assess 8(6):1253–65

Scinicariello F, Abadin HG, and Murray HE. 2011. Association of low-level blood lead and blood pressure in NHANES 1999–2006. Environ Res 111(8):1249–57

Sexton K, and Hattis D. 2007. Assessing cumulative health risks from exposure to environmental mixtures - Three fundamental questions. Environ Health Persp 115(5): 825–32

Smith AH. 1988. Epidemiologic input to environmental risk assessment. Arch Environ Health 43(2):124–9

Smith TJ. 2002. Issues in exposure and dose assessment for epidemiology and risk assessment. Hum Ecol Risk Assess 8(6):1267–93

ED_002191_00025139-00018

Stayner L, Steenland K, Greife A, *et al.* 1993. Exposure-response analysis of cancer mortality in a cohort of workers exposed to ethylene-oxide. Am J Epidemio 138(10): 787–98

Stayner L, Toraason M, and Hattis D. 2002. Risk assessment at the crossroads of the 21st century: Opportunities and challenges for research. Hum Ecol Risk Assess 8(6): 1195–202

Stayner L, Steenland K, Dosemeci M, *et al.* 2003. Attenuation of exposure-response curves in occupational cohort studies at high exposure levels. Scand J Work Environ Health 29(4):317–24

Stayner L, Vrijheid M, Cardis E, *et al.* 2007. A Monte Carlo maximum likelihood method for estimating uncertainty arising from shared errors in exposures in epidemiological studies of nuclear workers. Radiat Res 168(6):757–63

Steenland K, Deddens J, and Stayner L. 1998. Diesel exhaust and lung cancer in the trucking industry: Exposure-response analyses and risk assessment. Am J Indust Med 34(3): 220–8

Steenland K, Piacitelli L, Deddens J, *et al.* 1999. Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. J Natl Cancer I 91(9): 779–86

Steenland K, Sanderson W, and Calvert GM. 2001. Kidney disease and arthritis in a cohort study of workers exposed to silica. Epidemiology 12(4):405–12

Stewart WF and Correa-Villasenor A. 1991. False positive exposure errors and low exposure prevalence in community-based case-control studies. Appl Occupat Environ Hyg Appl Occupat Environ Hyg 6(6):534–40

Szklo MA and Nieto FJ. 2004. Identifying Noncausal Associations: Confounding. In: Epidemiology: Beyond the Basics, pp 177–210. Jones and Bartlett Publishers, Boston, MA, USA

Tellez-Plaza M, Navas-Acien A, Crainiceanu CM, *et al.* 2010. Cadmium and peripheral arterial disease: Gender differences in the 1999-2004 US National Health and Nutrition Examination Survey. Am J Epidemio 172(6):671–81

Tellez-Rojo MM, Bellinger DC, Arroyo-Quiroz C, *et al.* 2006. Longitudinal associations between blood lead concentrations lower than 10 microg/dL and neurobehavioral development in environmentally exposed children in Mexico City. Pediatrics 118(2):e323–30

Teschke K, Chow Y, Brauer M, *et al.* 2002. Exposures and their determinants in radiographic film processing. Aihaj 63(1):11–21

Thomas KW, Dosemeci M, Coble JB, *et al.* 2010. Assessment of a pesticide exposure intensity algorithm in the agricultural health study. J Expo Sci Environ Epidemiol 20(6): 559–69

USEPA (US Environmental Protection Agency). 2005. Guidelines for Carcinogen Risk Assessment. EPA/630/P-03/001F Risk Assessment Forum. Available at http://www.epa.gov/osa/mmoaframework/pdfs/CANCER-GUIDELINES-FINAL-3-25-05[1].pdf (accessed July 15, 2013)

USEPA. 2013. Human Health Risk Assessment. Available at http://epa.gov/riskassessment/health-risk.htm (accessed 16 September 2013)

Van Wijngaarden E. 2005. A graphical method to evaluate exposure-response relationships in epidemiologic studies using standardized mortality or morbidity ratios. Dose Response 3(4):465–73

Vandenberg LN, Colborn T, Hayes TB, *et al.* 2012. Hormones and endocrine-disrupting chemicals: Low-dose effects and nonmonotonic dose responses. Endocr Rev 33(3): 378–455

ED_002191_00025139-00019

VanderWeele TJ. 2009. On the relative nature of overadjustment and unnecessary adjustment. Epidemiology 20(4):496–9

Whittemore A. 1986. Epidemiology in risk assessment for regulatory policy. J Chron Dis 39(12):1157–68

Wigle DT and Lanphear BP. 2005. Human health risks from low-level environmental exposures: No apparent safety thresholds. PLoS Med 2(12):1232–4

Zhu M, Fitzgerald EF, Gelberg KH, *et al.* 2010. Maternal low-level lead exposure and fetal growth. Environ Health Perspect 118(10):1471–5

ED_002191_00025139-00020